Human Immunodeficiency Virus-Associated Nephropathy

THE KIDNEYS HAVE EMERGED as intriguing organs of involvement in patients infected with the human immunodeficiency virus (HIV). In addition to infections and neoplasms, HIV-associated nephropathy has become an important manifestation of HIV infection. This disorder typically presents with heavy proteinuria and progressive renal insufficiency without hypertension. The kidneys are large at the beginning and usually remain so during the course of the disease. On microscopic examination there are consistent abnormalities in the glomeruli, tubules, and interstitium. The glomerular lesion is of focal and segmental glomerulosclerosis, often in an early stage of evolution. Clusters of visceral epithelial cells are enlarged and coarsely vacuolated, and capillary walls are partially collapsed. Capillary lumina may contain foam cells. There is degeneration and necrosis of tubular epithelium. Many tubules are microcystically dilated and filled with plasma protein-containing casts; Bowman's spaces are dilated and contain the same material. The interstitium is edematous and is infiltrated by scattered lymphocytes. At the ultrastructural level, there is effacement of the foot processes of visceral epithelial cells. Tubuloreticular structures are widespread in all vascular endothelium and occasionally in mesangial cells and epithelial cells. Furthermore, nuclear bodies and granular and granulofibrillar transformation of nuclei are also found. Immunofluorescence reveals granular immunoglobulin M and complement deposits mainly in the abnormal glomerular segments.

Because the ultrastructural cellular abnormalities are often associated with viral infections, one of the major considerations for the pathogenesis of HIV-associated nephropathy is of direct viral infection of renal epithelium. Using a complementary DNA probe, we documented HIV genome in renal glomerular and tubular epithelium, suggesting that HIV may be important in the initiation or progression of this disorder. This observation, however, leads to many unanswered questions, among which are, How does virus enter the CD4-negative renal epithelium? Are other factors, including infection with other viruses and hereditary considerations, also necessary?

A number of clinical features are worth noting. More than 90% of reported patients are African American; about 50% are intravenous drug abusers. Renal disease may antedate the development of other features of HIV infection, such as acquired immunodeficiency syndrome (AIDS)-related complex and AIDS. Indeed, about a third of the currently diagnosed cases of HIV-associated nephropathy in the United States are in patients who are HIV carriers. It is not unusual for a pathologist to suggest that the HIV-antibody status of a patient be determined based on a characteristic and diagnostic constellation of structural abnormalities in a renal biopsy specimen obtained to assess heavy proteinuria and azotemia. Renal function rapidly deteriorates; in most patients, end-stage renal failure develops within 6 to 12 months.

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Fine-Needle Aspiration Biopsy in the Diagnosis of Pediatric Tumors

DIAGNOSING TUMORS in children presents a special set of circumstances in which the desire for diagnostic techniques of low morbidity and good patient acceptance must be balanced with requirements for high diagnostic accuracy. While fine-needle aspiration biopsy (FNAB) is a cost-effective technique with good patient acceptance, it has received limited acceptance among pediatricians as an initial diagnostic tool. The relative rarity and small cell nature of many pediatric neoplasms have caused pathologists to be uneasy with the cytologic diagnosis of these tumors. In addition, many palpable nodules in children represent reactive lymphoid proliferations difficult to separate from lymphoma or leukemia on purely morphologic grounds. Recent advances in the areas of immunocytochemistry, molecular biology, and DNA probe technology have improved the diagnostic accuracy of FNAB for the evaluation of these proliferations.

Diagnosing small round cell tumors of children by FNAB offers some advantages over diagnosis by open biopsy in that surgical excision may be delayed until after chemotherapy has reduced the tumor size. The limited size of the specimen obtained by FNAB, however, may deprive a treating oncologist of valuable information relating to histologic grade, tumor karyotype, and oncogene amplification status. Advances in tissue culture, oncogene identification, and immunocytochemical techniques have allowed the identification of chromosomal abnormalities, differentiation markers, and oncogene amplification in specimens obtained by aspiration. While FNAB is currently most useful in the diagnosis of recurrent or high-stage disease, future advances in molecular biology may allow FNAB to supply prognostic and therapeutic information now available only by open biopsy.

Fine-needle aspiration represents a simple method for separating patients with clinically suspicious adenopathy into surgical and nonsurgical candidates. The combination of morphologic analysis with immunocytochemical documentation of light-chain clonality appears highly accurate for distinguishing benign adenopathy from lymphomas. Patients with cytologically and immunohistochemically benign adenopathy may be observed attentively and patients with morphologically suspicious disease should undergo open biopsy. Following this scheme, the number of biopsies done for adenopathy can be reduced.

Fine-needle aspiration biopsy can yield valuable diagnostic information in various head and neck lesions. It has been shown to be an accurate method for evaluating thyroid nodules and can identify a variety of embryologic rests within the head and neck. The ease of FNAB coupled with its high diagnostic accuracy makes it a desirable method for diagnosing lesions arising in children.

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Molecular Mechanisms of Heart Muscle Disease

SUBCELLULAR MECHANISMS of dilated heart muscle disease (congestive cardiomyopathy) are poorly understood. With the development of techniques of molecular biology, some causal events in a specific form of congestive cardiomyopathy, the form induced by the anthracycline doxorubicin (Adriamycin) hydrochloride, have recently been elucidated. Postulated mechanisms of doxorubicin congestive cardiomyopathy include DNA intercalation, free-radical injury, lipid peroxidation, and mitochondrial damage. It has been shown that a relatively specific effect of doxorubicin use is selective changes in the expression of cardiac α-actin (α_c-actin) polypeptide and messenger RNA in vitro and by analogous studies in vivo. This selective defect in the expression of a critical sarcomeric protein may ultimately relate to the defective contractility in doxorubicin congestive cardiomyopathy.

Data show that doxorubicin has a relatively selective effect on the steady-state expression of α_c-actin mRNA compared with nonsarcomeric β-actin or glyceraldehyde-3-phosphate dehydrogenase mRNAs in the rat heart in vivo in both a dose-related and a temporal way in which the nadir acute doxorubicin effect occurred three days after therapy. It has been known for years that doxorubicin congestive cardiomyopathy is related to cumulative doxorubicin therapy. Many antineoplastic chemotherapy regimens use sequential doxorubicin administration, which may empirically correlate with recent in vivo- and in vitro-derived scientific data.

The defect in the expression of α_c-actin mRNA induced experimentally by doxorubicin may relate to cumulative toxic effects. We have initiated an experimental model for recovery of the heart from doxorubicin's cardiotoxic effects. In this model, cardioprotective agents are used to prevent doxorubicin cardiotoxicity. Preliminary data suggest that the effect of the drug on α_c-actin mRNA expression cannot be ablated by administering some cardioprotectant agents such as ICRF 187.

Molecular biologic methods have been applied more recently to the emerging problem of congestive cardiomyopathy in the acquired immunodeficiency syndrome (AIDS) to explore its subcellular mechanisms. Preliminary data suggest that zidovudine (AZT), the widely used antiretroviral drug, has an associated cardiotoxicity in rats that is manifested ultrastructurally by mitochondrial disarray in cardiac myocytes. The doses used in the experimental system were relatively high compared with those used in AIDS therapy at present. Future work will explore the molecular mechanisms of AZT cardiotoxicity by attempting to localize the molecular targets that may correlate with the observed cardiac ultrastructural changes induced by AZT by using methods adapted from doxorubicin-induced congestive cardiomyopathy models.

The pathogenetic mechanism of drug-induced congestive cardiomyopathy may not directly relate to a depressed expression of α_c-actin mRNA in the heart. Nonetheless, it is intriguing to find that depressed α_c-actin mRNA expression in the myocardium appears to relate pharmacologically to doxorubicin administration. Future studies may link doxorubicin-induced congestive cardiomyopathy mechanistically with defects in the expression of sarcomeric proteins and mRNAs, particularly α_c-actin. Studies of models of the disorder provide a better understanding of the molecular mechanisms that are involved in the regulation of myocardial actin homeostasis in health and potential derangements in heart muscle disease.

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Hepatitis C Test

NON-A, NON-B HEPATITIS, defined as hepatitis resulting from infection with agents other than the hepatitis A or B viruses, is the most frequent transfusion-associated infection in the United States and a major cause of transfusion-related morbidity and mortality. Studies in the late 1970s showed that non-A, non-B hepatitis developed in as many as 10% of transfusion recipients. Although the acute infection is usually asymptomatic, chronic liver disease will develop in 50% of infected patients, and in 20% of these, cirrhosis may develop. In the absence of a specific test for the causative agent of non-A, non-B hepatitis, blood banks in the mid-1980s began screening donors for elevated levels of alanine aminotransferase (formerly glutamic-pyruvic transaminase) and antibody to the hepatitis B core protein. These tests were predicted to identify 30% to 40% of infectious blood donors.

Transmissivity studies in animals indicated that the major causative agent of non-A, non-B hepatitis was a small RNA virus, although many attempts to isolate this agent were unsuccessful. Recently investigators at the Chiron Corporation and the Centers for Disease Control took a novel approach and synthesized components of this virus using recombinant DNA technology. The investigators isolated nucleic acid from the plasma of a chimpanzee with non-A, non-B hepatitis and inserted pieces of this material into bacteria. Of 1 million recombinant bacterial colonies screened, 1 expressed a protein recognized by antibodies from patients with non-A, non-B hepatitis. The genetic insert in this colony was identified, and a larger genetic clone containing this sequence was then inserted into yeast. The recombinant protein produced by this yeast, called the C100-3 protein, is the basis for the hepatitis C virus (HCV) screening test licensed by the Food and Drug Administration (FDA) on May 2, 1990.

The HCV screening test detects antibodies that bind to the C100-3 protein. A large majority of patients with chronic non-A, non-B hepatitis, both transfusion-associated and non-transfusion-associated, have antibodies to this protein. The